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DOI: https://doi.org/10.21037/lcm.2018.03.01

Hormesis and dose-responses in herbal traditional Chinese medicine (TCM) alone are insufficient solving real clinical TCM challenges and associated herbal quality issues

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Provenance: This is a editorial commissioned by the Editor-in-Chief, Zhen Xiao, MD, MPA (Longhua Hospital Shanghai University of Traditional Chinese Medicine, Shanghai, China).

Comment on: Wang D, Calabrese EJ, Lian B, *et al.* Hormesis as a mechanistic approach to understanding herbal treatments in traditional Chinese medicine. Pharmacol Ther 2018;184:42-50.

Received: 16 February 2018; Accepted: 02 March 2018; Published: 21 March 2018.

doi: 10.21037/lcm.2018.03.01

View this article at: http://dx.doi.org/10.21037/lcm.2018.03.01

Traditional Chinese medicine (TCM) products, as herbal treatment options for minor illnesses or functional ailments, have a long history in China and other Asian countries (1-6), and are used as complementary medicine even for more serious diseases in other countries including Germany (7). However, efforts of its worldwide distribution are limited as are attempts to integrate herbal TCM in modern medicine and vice versa (8-10), with few exemptions (11). Indeed, scientific and public pressure on herbal TCM as therapy alternative for significant diseases continues to focus among other difficulties on communicable details of clear recommendations how to use herbs as part of the TCM. To resolve some of these problems, hope came up with the recent publication on hormesis by Wang *et al*. (12). In principle, this report considers hormesis as a mechanistic approach to understand herbal treatments in TCM, whereby herbal TCM medicines may act through hormetic dose-response mechanisms reflecting components that are stimulatory at low doses and inhibitory at high doses *in vitro*. To overall disappointment, however, concrete clinical recommendations for individual diseases or herbs were only marginally provided that would allow guidance of physicians or establishing guidelines of clinical management. Similarly, poorly practicable but interesting to read are theoretical discussions about the complex TCM-related "Monarch, Minister, Assistant and Guide" system that vaguely attributes different qualifications to not further specified TCM herbs (12). For instance, it remains unclear for what a Monarch herb stands and how this can be transferred to clinical medicine that asks for established treatment guidelines and practicable solutions of dosage recommendations. However, these cannot be provided because ancient TCM philosophy proposes for prescribed TCM herbs to be tailoring to the patient's symptoms, signs and constitution (13,14), whereby original Chinese formulae are often modified, and such tailoring details are rarely available (14).

Apart from hormesis issues proposed already 15 years ago (12) and adapted in 2017 (15), various other aspects related to herbal TCM treatment modalities have been poorly handled in the past and are of high importance, requiring new pragmatic approaches in order to convince both, potential consumers and the scientific community, from its potential benefit(s) (*Table 1*) (6-11,13,14,16-18).

Table 1 Suggestions for improvements related to herbal TCM treatment

Suggestions for improvements	References
RCTs are needed to evaluate efficacy and risks of herbal TCM treatment	Wang *et al.*, 2007 (16); Teschke *et al.*, 2015 (14)
For assessing possible rare adverse events such as liver injury, prospective studies are required for valid data	Melchart *et al.*, 2017 (7)
Clinical data, relevant review articles, meta-analyses, and reports of RCTs should be presented in English language journals	Han *et al.*, 2018 (17)
Indications should be transferred from Chinese traditional concepts and diagnosis to worldwide accepted ICD diagnoses	Melchart *et al.*, 2017 (7)
Contraindications are to be defined	Teschke *et al.*, 2015 (14)
Treatment modalities need definition including form of application, daily dose and duration of use	Melchart *et al.*, 2017 (7)

TCM, traditional Chinese medicine; RCT, randomized controlled trials; ICD, international classification of diseases.

A crucial point are randomized clinical trials (RCTs), commonly considered as gold standard for assessing efficacy with abundant results published since 1990 (6,14,16,18). For instance, with the search terms of "TCM herbs and randomized controlled trial", publications in PubMed were identified in April 2016 with increasing annual frequencies since 1990 and an unexplained drop from 2014 to 2015 (18). As discussed in detail previously (6,14,16,18), low study quality was reported in virtually all RCTs of the overall TCM spectrum (16,18), which included in the majority herbal TCM but the trials of herbal interventions failed to completely report specific characteristics of the herbal products used (16). Respective analyses were based on abundant trials, with publications ranging from 10,000 (18) to 26,236 (16). As an example, one of these studies was based on an analysis of trial results published from 1999 to 2004 (16). Among 37,252 Chinese language articles identified in TCM journals published in mainland China, clinical trials were recognized in 26,263/37,252 articles, corresponding to 70.5%. Among these 26,263 clinical trials, 7,422 were initially identified as RCTs, equivalent to 28.3%, but of the 7,422 trials only 1,329 trials (17.9%) were truly randomized (16). In addition, some important methodological components of the RCTs were incompletely reported, such as sample size calculation (reported in 1.1% of RCTs), randomization sequence (7.8%), allocation concealment (0.3%), implementation of the random allocation sequence (0%), and intension to treat analysis (0%) (16). All reports were searched according to guidelines of the Cochrane Centre, and a comprehensive quality assessment of each RCT was completed using a modified version of the Consolidated Standards of Reporting Trials (CONSORT) checklist. Due to lacking data, uncertainty also prevails whether herbal TCM are at least equally or even more effective than conventional drugs. These shortcomings lead to the overall conclusion that the scientific quality of most published RCTs is limited and not suitable to propose treatment efficacy of TCM.

Another point of concern regarding herbal TCM is the highly variable quality of herbal products (*Table 2*) (19-22). This issue may start with the understanding of plant physiology and considering plant circadian rhythms as being critical to manufacture good quality of herbal products. The circadian clock system in plants controls day by day different and major metabolic pathways and functions including photosynthesis, stomatal opening, and molecular processes leading to gene expression (19,20). Considering circadian rhythms may be an option to improve plant quality (20). Of note, identifying clock controlled pathways and processes require multidisciplinary efforts (19). In addition, herbal product quality is strikingly influenced by biotic and abiotic plant stress affecting higher plants (21). In detail, biotic stress is caused by pathogen attacks of other living organisms such as insects and larger grazing animals, parasites, bacteria, viruses, and funghi. As opposed, abiotic stress is of environmental origin and triggered by heavy UV radiation, draft, wounding, or soil contamination by salts or heavy metals. Plant stress leads to oxidative stress through generation of free radicals including reactive oxygen species (ROS), it damages the integrity of the plant, and it is often the cause of limited herbal product quality. Emphasis should also be put on technical details such as extraction media used to prepare herbal products. Most traditional herbal medicines are decoctions and therefore water based

Table 2 Required improvements of herbal traditional Chinese medicine (TCM) product quality

Critical quality issues of herbal TCM products	References
To improve herbal product quality, consideration should be paid in the future to plant physiology with its circadian clock system	Teschke *et al.*, 2018 (19); Dakhiya *et al.*, 2017 (20)
Plant stress due to production of reactive oxygen species (ROS) is increasingly considered as cause of suboptimal plant quality	Teschke *et al.*, 2018 (19); Xuan *et al.*, 2016 (21)
Factors such as seasonal variation and areas of harvest should be more considered to keep plant quality at a high level	Teschke *et al.*, (19)
Herbal product quality may be altered depending on the used solvent	Xuan & Teschke, 2015 (22)
Plant quality depends among others on seasonal variation with time of harvest, and on area of harvest	Teschke *et al.*, 2018 (19)
Avoidance of treatment with herbal TCM products that are contaminated by impurities, misidentified herbs, or heavy metals like Lead, Cadmium, Mercury, and Arsenic or adulterated by conventional drugs	Melchart *et al.*, 2017 (7); Teschke *et al.*, 2018 (19); Melchart *et al.*, 2016 (23)
Mandatory use of analytical procedures in TCM products for authenticity, international botanical nomenclature and modern scientific based processing of raw drugs	Melchart *et al.*, 2016 (23); Melchart *et al.*, 2017 (7)

products. Nevertheless, regulators should clearly define for each herbal medicine the obligatory solvent for product manufacturing to ensure some degree of product uniformity. Indeed, there are substantial differences of phytochemical yield depending on the solvent used that include in addition to water also the synthetic products acetone, chloroform, methanol, and hexane (22).

Plant quality is also dependent on seasonal variation and area of harvest, as discussed and referenced in detail (19). For instance, this dependency on the harvest time was shown recently for the roots of *Cyathula officinalis*, a popular herbal TCM. Using a metabolomic approach based on gas chromatography-mass spectrum, 166 metabolites had been identified in these roots, 63 of which showed significant quantitative changes in different growth years of up to four years. It was suggested to harvest in the fourth grow year in order to boost herbal quality and extending these studies to other plants. Such studies about variation of phytochemicals in different harvest times are in line with Good Agricultural Standards of Chinese traditional herbs in China. Fixing the harvest year will provide consistency of batches and herbal products with the desired phytochemicals as target ingredients (19). Initially unexpected were results obtained with *Polygonum multiflorum* (PM), harvested from various regions of China and assessed for its hepatotoxic potential (19). This is of importance because PM is much used in China and elsewhere, known for its risk of liver injury. Indeed, liver toxicity was different among the various areas of harvest, and the most toxic PM was from the Sichuan Province. Studies also revealed that emodin was not considered the main hepatotoxin anymore, as opposed to previous studies. Preference is now given to both, tetrahydroxystilbene-O-(galloyl)-hex and emodin-O-hex-sulfate as the primary offending agents (19).

Among the unresolved clinical challenges, toxicity risks are associated with the use of herbal TCM (*Table 2*), especially reported cases of liver injury with partially high frequencies (6). Whereas the etiology of liver injury is clear in patients from China who used TCM herbs that contained unsaturated pyrrolizidine alkaloids (PAs) and developed typically the hepatic sinusoidal obstructive syndrome (SOS), the pathogenic background of liver injury by other TCM herbs often remains unclear and might partially be attributed to impurities or adulterants, requiring further analyses (*Table 2*) (6,19).

As opposed to literature data (6), results of a recent study revealed a very low incidence of liver injury among patients treated with herbal TCM (7). This report from Germany presented for the first time liver injury data derived from a prospective, hospital based and large scale study of 21,470 patients, who had no liver disease prior to treatment with herbal TCM (7), in which product falsification and adulteration were excluded (7,23), commonly found in other TCM products (19). Products used in the German hospital were also screened for microbial contaminations, aflatoxins, pesticides, and the heavy metals Lead, Cadmium, Mercury, and Arsenic (7,23). Among the 21,470 patients under herbal TCM treatment, 26 patients (0.12%) experienced abnormal serum liver values of alanine aminotransferase (ALT) ≥5 × ULN (upper

limit of normal), namely 300.0±172.9 U/L, mean ± SD, suggesting mild to moderate degrees of liver injury (7). Case evaluation was completed with respect to causality, assessed with the Roussel Uclaf Causality Assessment Method (RUCAM) in all 28 patients. RUCAM-based causality for TCM herbs was probable in 8/26 patients, possible in 16/26, and excluded in 2/26 cases. This study was carried out from 1994 to 2015 and showed 24 liver injury cases with a possible or probable RUCAM grading, corresponding to 24/21,470 cases and a tentative incidence rate of around 1.1‰. The low number of newly detected liver injury cases (7) is at variance to the large lists of liver injury cases presumably related to herbal TCM treatment, published mainly in Asian countries (6,19). It is unclear whether the high quality standard applied to the herbal TCM products used in the German hospital may have contributed to the low number of liver injury cases (7,19,23).

Our editorial hopefully encourages scientists and regulators to improve overall conditions of herbal TCM treatment by providing more evidence for a favourable benefit to risk constellation. In fact, China is rich in biologically active plants, which grow over a large fascinating landscape and provide abundant active molecules, favoring the early development of local herbal TCM (24). About 13,000 herbal preparations are used, listed in the Chinese Materia Medica (CMM), and available in China; they are officially recognized and described in detail by the Chinese Pharmacopeia, including herbs that are commonly used or represent regional variations and folk medicine variants. The Chinese Materia Medica is a reference book that also describes details of thousands of plant preparations, including some nonbotanical elements such as animal parts and minerals, which are incorrectly classified as herbal medicines. Outside of China, only around 500 Chinese herbs are commonly used. The plants of the Chinese Materia Medica contain multiple molecules as hidden champions for the development of potent drugs to be synthetized by the pharmaceutical industry.

Needless to say, the reputation of herbal TCM has substantially gained within the past few years, achieved through research on developing new drugs including artemisinin, as discussed and referenced in detail (6,19,25); a short summary on the discovery and development of artemisinin is warranted as encouragement to younger scientists how good scientific work can be achieved (6,19). The Nobel Prize for Medicine or Physiology 2015 will certainly further inspire modern TCM research in the near future, although the Nobel Prize committee did not specify that the prize be to TCM. Instead, the 2015 Nobel Prize awarded Youyou Tu as scientist for her pioneering work of drug development originating from herbal TCM and her discovery of artemisinin for the treatment of malaria. Artemisinin is derived from the herbal TCM Qing Hao (*Artemisia annua* L.), known since more than two thousand years as a Chinese herbal medicine for various ailments. The initial breakthrough in the discovery of artemisinin dates back to 4 October 1991, when an extract derived from *Artemisia annua* was found 100% effective against parasitemia in mice infected with *Plasmodium berghe*i and in monkeys with *Plasmodium cynomolgi*. After ascertaining that the extract was safe for human use, clinical efficacy was tested in the Chinese Hainan province in trials with patients infected with both *Plasmodium vivax* and *Plasmodium falciparum*. The results were encouraging: patients treated with the extract experienced rapid disappearance of symptoms such as fever and decrease of parasitemia, whereas patients receiving chloroquine did not. Artemisinin and its derivatives such as artesunate and artemether are now successfully used to treat patients with malaria by *Plasmodium vivax* or *Plasmodium falciparum*, preferring a combination with antimalarial drugs other than artemisinin, called artemisinin-based combination therapies (ACTs), and banning artemisinin-based monotherapy that may promote the risk of antimalarial drug resistance. Malaria is transmitted among humans by female mosquitoes of the Anopheles genus, which take blood meals from patients with malaria to carry out egg production; such blood meals are the link between the human and the mosquito hosts in the parasite life circle and enable transfer malaria through biting humans by infected mosquitoes. Based on treatment with ACTs together with other approaches such as use of insecticides and insecticides-treated mosquito nets, the WHO stated that the number of patients with malaria and malaria-related mortality has been drastically reduced within the past years, and there is no question that most of this improvement is attributable the work of Youyou Tu with *Artemisia annua*.

From the TCM herb *Artemisia annua* to the active molecule and the beneficial drug was a long but successful way of drug research and development. This is not in line with mainstream philosophy of herbal TCM that prefers the use of a bundle of herbs rather than to focus on a single herb or even a single molecule, as opposed to what Youyou Tu did. In 1996 she started her project against malaria by investigating more than 2,000 Chinese herbal preparations and identified 640 hits that had possible antimalarial hits.

More than 380 extracts obtained from around 200 herbs were evaluated, and a high antimalarial activity was found in an extract derived from *Artemisia annua* as prepared according to "A Handbook of Prescriptions for Emergencies" by Ge Hong (248–346 AD). Originating from artemisinin with a molecular weight of 282 Da and a molecular formula of $C_{15}H_{22}O_5$, dihydroartemisinin was found to be more stable and ten times more effective than artemisinin, and adding a hydroxyl group to the molecule provided more opportunities for developing new artemisinin derivatives through esterification. The fascinating route from a TCM herb via a molecule to a drug is finally highlighted again at the molecular level, now in the human erythrocytes infected with plasmodia. The molecular basis of treatment efficacy includes among several mechanisms the cleavage of artemisinin's endoperoxide bridge by a Fe(II) Fenton, which is facilitated by heme-iron originating from hemoglobin degradation in the parasites' food vacuoles. Autodigestion of plasmodium food vacuoles is achieved following their damage by hydroxyl radicals and superoxide anions. Consequently, artemisinin with its derivatives is a drug with a specific molecular target in a specific parasitic disease; toxicity has not been found in clinical studies with normal doses. Expectations are high that more hidden drug champions can be derived from herbal TCM with high efficacy and little harm, providing a favorable benefit-risk profile.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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doi: 10.21037/lcm.2018.03.01
Cite this article as: Teschke R, Melchart D, Xuan TD. Hormesis and dose-responses in herbal traditional Chinese medicine (TCM) alone are insufficient solving real clinical TCM challenges and associated herbal quality issues. Longhua Chin Med 2018;1:3.

